FORM PTO-1390 (REV 10-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 11020-55

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/763666

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US99/19307	August 25, 1999	August 25, 1998

TITLE OF INVENTION
METHOD OF ENHANCING CATHETER PATENCY USING A CITRATE SALT CATHETER LOCK SOLUTION

APPLICANT(S) FOR DO/EO/US
Stephen R. ASH

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. [X] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [X] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). unsigned
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    a. PCT Request
    b. Intetnational Publication
    c. Receipt of Demand for International Preliminary Examination
    d. International Preliminary Examination
    e. PCT/IB/332,304,308
    f. [illegible]

Express Mail Label No.: EL414478247US
Date of Deposit: 23 February 2001
I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.
Linda S.W. Conrad
Signature of person mailing paper or fee

JC02 Rec'd PCT/PTO 23 FEB 2001

U.S. APPLICATION NO	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/763666	PCT/US99/19307	11020-55

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1000.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $860.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $710.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $690.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 100.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	43 - 20 =	23	X $18.00	$ 414
Independent claims	8 - 3 =	5	X $80.00	$ 400
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$
TOTAL OF ABOVE CALCULATIONS =				$ 914
[X] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$
SUBTOTAL =				$ 457
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$ 457
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$
TOTAL FEES ENCLOSED =				$ 457.00
			Amount to be refunded:	$
			charged:	$

a. [X] A check in the amount of $ 457.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-3030. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pendin g status.

SEND ALL CORRESPONDENCE TO

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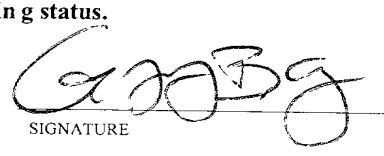

SIGNATURE

Gregory B. Coy

NAME

#40,967

REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:	)	
	)	Before the Examiner
Stephen R. Ash	)	
	)	
Serial No. Not Yet Known	)	
	)	Group Art Unit
Filed: February 23, 2001	)	
	)	
METHOD OF ENHANCING CATHETER PATENCY USING A CITRATE SALT CATHETER LOCK SOLUTION	)	February 23, 2001

PRELIMINARY AMENDMENT

Honorable Commissioner of Patents
Washington, DC 20231

Sir:

As a Preliminary Amendment to the attached U.S. national stage patent application, please enter the following amendments prior to computation of the filing fee.

IN THE CLAIMS:

Please amend claims 5-8, 13-18, 21-25, 27-29, 32-34 and 41-43 as follows:

5. (Amended) The method of [any of claims 1-4] claim 1 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

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6. (Amended) The method of [any of claims 1-5] claim 1 wherein the lock solution has a pH level between about 4.5 and about 6.5.

7. (Amended) The method of [any of claims 1-6] claim 1 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

8. (Amended) The method of [any of claims 1-7] claim 1 wherein the catheter has an internal volume and said adding includes injecting the catheter with an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

13. (Amended) The method of [any of claims 9-12] claim 9 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline or mixtures thereof.

14. (Amended) The method of [any of claims 9-13] claim 9 wherein the lock solution has a density of between about 1.02 g/ml to about 1.04 g/ml and a viscosity of between about 1.5 cP and about 4.0 cP.

15. (Amended) The method of [any of claims 9-14] claim 9 wherein the lock solution has a density of between about 1.02 g/ml and about 1.03 g/ml a viscosity of between about 1.5 cP and about 2.0 cP.

16. (Amended) The method of [any of claims 9-15] claim 9 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

17. (Amended) The method of [any of claims 9-16] claim 9 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

18. (Amended) The method of [any of claims 9-17] claim 9 wherein the lock solution has a pH level between about 4.5 and about 6.5.

21. (Amended) The method of claim 19 [or 20] wherein the bactericidal component includes greater than about 90%, by weight based on the weight of the bactericidal component, of a citrate salt.

22. (Amended) The method of [any of claims 19-21] claim 19 wherein the lock solution includes a viscosifying agent.

23. (Amended) The method of [any of claims 19-22] claim 19 wherein the pharmaceutically acceptable lock solution has a pH between about 4.5 and about 6.5.

24. (Amended) The method of [any of claims 19-23] claim 19 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

25. (Amended) The method of [any of claims 19-24] claim 19 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

27. (Amended) The device of claim 26 wherein said lock solution [comprising] comprises a sodium citrate salt.

28. (Amended) The device of claim 26 [or 27] wherein the lock solution comprises a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

29. (Amended) The device of [any of claims 26-28] claim 26 wherein the lock solution has a density of between about 1.0 and about 1.5 and a viscosity of between about 1.5 cP and 4.0 cP.

32. (Amended) The device of claim 30 [or 31] wherein the lock solution has a pH level between about 4.5 and about 6.5.

33. (Amended) The device of [any of claims 30-32] claim 30 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

34. (Amended) The device of [any of claims 30-33] claim 30 wherein the lock solution has a density between about 1.0 and about 1.5 and a viscosity between about 1.5 cP and about 4.0 cP.

41. (Amended) The composition of claim 39 [or 40] wherein the lock solution includes, in weigh percent, about 10% to about 40% of the citrate salt.

42. (Amended) The composition of [any of claims 39-41] claim 39 wherein the citrate salt is trisodium citrate.

43. (Amended) The composition of [any of claims 39-42] claim 39 comprising heparin.

Respectfully submitted

By: _____

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11020-55:GBC:119053

METHOD OF ENHANCING CATHETER PATENCY USING A CITRATE SALT CATHETER LOCK SOLUTION

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of United States Provisional Application Serial No. 60/097,777 filed on August 25, 1998, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention generally relates to intravascular infusion devices and methods of enhancing the patency of intravascular catheters. More specifically but not exclusively, this invention relates to infusing a lock solution into an indwelling intravascular catheter and to methods of inhibiting infection in an animal having an indwelling intravascular catheter.

BACKGROUND OF THE INVENTION

Catheters are used with increasing frequency to treat patients requiring a variety of medical procedures. The catheters offer many advantages for patients; for example, catheters provide ready access without repeated injections for administration of large volumes of fluids, nutrients, medications and withdrawal of blood. The catheters can either be acute or temporary for short-term use or chronic for long-term treatment. They are commonly inserted into central veins (such as the vena cava) from peripheral vein sites. Great care must be taken in the placement and use of a chronic catheter to prevent infection of the patient at the site of access or within the vascular system. Chronic venous catheters usually contain a DACRON cuff attached to the catheter and placed under the skin, which promotes ingrowth of fibrous tissue, fixes the catheter in position, and prevents bacterial migration around the catheter.

Catheters can be used for infusion of fluids, such as, for example, drugs, electrolytes or fluids used in chemotherapy, or for the removal of blood on an intermittent basis. For example, in hyperalimentation treatment, the catheters are usually used for infusion of large volumes of fluids. In chemotherapy, catheters are used for infusion of drugs on an intermittent basis, ranging from daily to weekly. For hemodialysis, dual-lumen catheters are used--usually three times per week; one lumen allows removal of blood, while the other lumen allows blood to return. However, catheters, especially chronic catheters, have drawbacks. They can become occluded by a thrombus, and even if extreme care is

taken, the catheters can increase a patent's risk of infection.

In order to prevent clotting of the catheters between uses, the catheters are usually filled with a lock solution that comprises a concentrated solution of the commonly used anticoagulant, heparin (up to 10,000 units of heparin per catheter lumen). The heparin lock solution is injected into each lumen immediately after each use, and preferably left in the catheter until the catheter is accessed again. The heparin lock solution must be withdrawn from the catheter before the next use because infusing this amount of heparin in a patient might result in excessive bleeding.

However, even with the use of a heparin lock solution, the catheter can become occluded between uses from coagulation of blood in the catheter. Blood may be found in the catheter because, for example, an inadequate volume of heparin was infused within the catheter lumen, the heparin diffused from the lumen, or residual blood remains in the lumen. This often results in formation of a thrombus with concomitant loss of flow through the lumen. The occluded catheters frequently are removed and/or replaced.

Since catheters are inserted into veins or arteries, they bypass the protective dermis layer, and provide direct access to a patient's blood stream. This can cause the inadvertent transfer of infectious agents into the vein or artery at the location of the catheter. In addition, the foreign surfaces of catheters can create a smooth surface at which bacteria can grow, and at which the white cells are unable to surround or "phagocytize" the bacteria.

Heparin has no anti-bacterial properties and, in fact, may help to promote growth of bacteria within the "biofilm" layer of protein on the catheter surfaces (protamine has the opposite effect). The "biofilm" proteins on the catheter surfaces can protect bacteria from antibiotics and white cells. Also, heparin induces the loss of platelets and, paradoxically, can induce clotting in some patients (the "white clot" syndrome). Since catheters, particularly venous catheters, are frequently accessed with syringes, or uncapped and directly connected to IV lines, they have a propensity to become contaminated. If there is bacteremia (bacteria in blood), then the catheter surfaces within the vein or artery can become seeded with bacteria. In either case, the patient can develop septicemia (infection in the blood) and become seriously ill. Often these patients must be hospitalized and given intravenous antibiotics. In spite of this care, patients often remain seriously ill until the infected catheter is removed.

Thus in light of the above described problems, there is a continuing need for advancements in the relevant field, including improved methods, composition and devices relating to enhancing the patency of indwelling intravascular catheters. The present invention is such an advancement and provides a wide variety of benefits and advantages.

SUMMARY OF THE INVENTION

The present invention relates to catheter lock solutiona, intravascular infusion devices for infusing a lock solution into patient and to methods for enhancing the patency of intravascular catheters. Various aspects of the invention are novel, nonobvious, and provide various advantages. While the actual nature of the invention covered herein can only be determined with reference to the claims appended hereto, certain forms and features, which are characteristic of the preferred embodiments disclosed herein, are described briefly as follows.

In one form, the present invention provides a method of treating patients having an indwelling intravascular catheter. The method comprises selecting a patient having an indwelling intravascular catheter defining a lumen therethrough and having an infection or a substantial risk of infection related to the presence of the catheter; and infusing a catheter lock solution into the lumen. The solution comprises a citrate salt solution having a concentration effective to eliminate infection and to reduce the likelihood of subsequent infection. In one embodiment, the citrate salt can be included in the catheter lock solution in a concentration preferably within the range, in weight percent, of about 1.5% to about 50%. The catheter lock solution can include a viscosifying agent such as polyethylene glycol, glycerin, polyglycerin or mixtures thereof. In an alternative embodiment, the lock solution is prepared to have a pH level lower than about 6.5, more preferably between about 4.5 and about 6.5.

In another form, the present invention includes a method of inhibiting infections in an animal having an indwelling catheter defining a lumen therethrough. The method comprises infusing into the lumen a pharmaceutically acceptable lock solution including a compound having anticoagulant and antibiotic activity. The lock solution has a density and a viscosity sufficient to maintain the lock solution in the lumen for a desired amount of time. Preferably the lock solution has a viscosity of from about 1.5 cP to about 4.0 cP. In one embodiment the lock solution includes the citrate salt in a hypertonic concentration, preferably in a concentration between about 1.5 and about 6.5. In another embodiment the lumen of the catheter has an internal volume and a sufficient amount of the lock solution is infused into the lumen, to fill, in percent by volume, between about 80% and about 100% of the internal volume of the lumen.

In yet another form, the present invention provides a method of treating animals that exhibit a risk of infection and having a surgically implanted catheter. The method comprises adding a pharmaceutically acceptable lock solution comprising a bactericidal component into the catheter. The bactericidal component includes greater than about 50 wt%, based on the weight of the bactericidal component, of a citrate salt. In preferred embodiments, the pharmaceutically acceptable lock solution is prepared to be sufficiently caustic to substantially inhibit the growth of bacteria and microorganisms in the lumen.

In still yet another form, the present invention includes an infusion device for infusing a lock solution into a lumen of a catheter. The infusion device includes

a syringe and a catheter lock solution contained in the syringe. The lock solution is preferably a pharmaceutically acceptable solution comprising a citrate salt, and the syringe containing the solution is preferably sterilized. The solution may also include a viscosifying agent to provide to the lock solution sufficient viscosity and density to remain in the lumen for a desired amount of time. In preferred embodiments, the lock solution has a density of between about 1.0 g/ml and about 1.5 g/ml and a viscosity between about 1/5 cP and about 4.0 cP.

In still another form, the present invention provides a kit for accessing a patient's intravascular system. The kit comprises: a catheter defining therethrough at least one lumen; a container; and a catheter lock solution contained within the container, the solution comprising a citrate salt solution.

In yet another from, the present invention provides a catheter lock solution. The lock solution includes, in weight percent, about 1.5% to about 50% of a citrate salt, and an amount of a viscosifying agent sufficient provide the lock solution with a viscosity of from about 1.0 cP to about 4.0 cP.

Further objects, features, aspects, forms, advantages and benefits shall become apparent from the description and drawings contained herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of one embodiment of a catheter and syringe for infusing a lock solution into a catheter for use with the present invention.

FIG. 2 is a graph plotting monthly incidence of sepsis in all patients of a hemodialysis unit.

FIG. 3 is a graph plotting the number of vials of urokinase used for catheter occlusion per month in a hemodialysis hospital unit.

FIG. 4 is a graph plotting the longevity of one embodiment of a tunnel catheter for use with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to the embodiments illustrated herein and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended. Any alterations and further modifications in the described processes, systems or devices, and any further applications of the principles of the invention as described herein, are contemplated as would normally occur to one skilled in the art to which the invention relates.

In one form, the present invention provides a catheter having retained therein a lock solution. The lock solution enhances the patency of the catheter and exhibits anti-coagulation and antibiotic activity. The lock solution provides particular advantages by increasing the longevity of catheters, reducing incidence of catheter occlusion, and reducing incidence of sepsis or bacterial infection in the patient. In addition, the lock solution of the present invention can be used with or without other anticoagulant agents and/or other antibacterial agents. Further, certain lock solutions of the present invention can be infused into the patient from the catheter in preparation for a subsequent use of the catheter without the necessity of withdrawing the lock solution from the catheter before infusion of additional fluids or medications.

In another form, the present invention provides a method of enhancing the patency of a catheter. The method includes infusing into the catheter a lock

solution selected in accordance with the invention and allowing the lock solution to remain in the catheter for a desired amount of time between catheter uses.

The catheters for use with the present invention typically can either be acute (temporary) or chronic (long-term) catheters surgically implanted in the animal. The catheters usually are inserted into a vein or artery. The catheters are typically used in varying intervals to administer fluids, nutrients, and medications into the body. The catheters also can be used to withdraw body fluids, such as blood, for hemodialysis treatment. When not in use, the catheter remains in its intravascular position until subsequent treatment is preferred

The catheters used accordance with this invention include known and commonly used catheters and are readily available from a variety of commercial sources. The catheters may vary in configuration and size. One type of catheter commonly used in accordance with this invention is a tunneled catheter that includes a cuff for ingrowth of tissue to anchor the catheter. Examples of catheters that may be used include, but are not restricted to, an ASH SPLITCATH by Ash Medical of West Lafayette, Indiana; TESIO and ASH CATHETERS by Medcomp of Harleysville, Pennsylvania; PERM CATH by Quinton Instrument Company of Seattle, Washington; HICKMAN and VAS CATH by Bard, Inc. of Salt Lake City, Utah. Catheters containing totally subcutaneous ports are also useful in the present invention; examples include LIFESITE by Vasca of Topsfield, Maine, and DIALOCK by Biolink, Inc. of Boston, Massachusetts.

FIG. 1 depicts one example of a catheter 10 for use with this invention. Catheter 10 is a dual lumen catheter and includes an outer sheath 12 having a cuff 38

and first and second lumens 14 and 16, respectively. Lumens 14 and 16 extend from distal tip 18 through sheath 12 and exit from sheath 12 at connection 36. Each of lumens 14 and 16 include releasable clamps 20 and 22, respectively. Each of lumens 14 and 16 terminate in a threaded end 24 and 26, which can be threadedly attached to protective end caps 28 and 30, respectively. Fluids including a lock solution can be infused or withdrawn from each lumen 14 and 16 by inserting needle 32 of a syringe 34 through protective end caps 28 and/or 30 after protective end caps 28 and/or 30 have been sterilized by cleaning successively, for example with betadine and alcohol. Alternatively, one or both protective end caps 28 and 30 can be removed and threaded ends 24 and 26 can be threadedly attached via a connector (not shown) to lines for infusion or withdrawal of fluids (not shown). Once a desired treatment session has been completed, the needles are removed or the connectors are replaced with fresh, sterile protective end caps. The lumens are then typically flushed with normal saline, after which a lock solution is injected into each lumen. All procedures are performed using standard sterile techniques well known to those skilled in the art. The catheters for use with this invention can be prepared from a variety of materials, including, for example, silicon, polyurethane, polyvinyl, silicone, or silastic elastomer.

Chronic catheters are usually inserted through an internal jugular vein into the superior vena cava. Usually these catheters include a cuff attached to the exterior of the catheter and placed under the skin, which promotes ingrowth of fibrous tissue, and thus fixes the catheter in position and prevents bacterial migration around the catheter. While the catheters are

manufactured to function for several months, for example, TESIO catheters can last for up to four years with proper intervention, in actual practice, the catheters, prior to the present invention, have exhibited limited longevity because of occlusion and/or infection. These catheters frequently must then be removed and/or replaced.

As mentioned above, in order to prevent clotting of catheters between use, catheters are commonly filled with lock solutions comprising an anticoagulant agent and sometimes a second agent having antibacterial properties. It has unexpectedly been determined that citrate salt solutions as described herein exhibit surprisingly effective antibacterial activity. In a series of tests, with a variety of bacterium spores injected into a 47% solution of citrate salts, a six-log kill is obtained in seven days for E.coli and P.aeruginosa, and in 21 days for S.Aureus.

In accordance with the invention a catheter lock solution comprising a citrate salt is used to increase the patency of implanted catheters. As used herein, the term "lock solution" refers to a solution that is injected or otherwise infused into a lumen of a catheter and with the intention of allowing a substantial portion of a lock solution to remain in the lumen until it is desired or required to access that particular lumen again, typically for additional treatment, i.e., infusion or withdrawal of fluid. Preferably the lock solution can remain in the lumen for a desired amount of time lasting from about 1 hour to 3 or 4 days or longer. However, frequently the lock solution is changed on a daily basis during regular care and sterile maintenance of the indwelling catheter. Use of a lock solution of the present invention provides particular advantages for

patients with catheters by prolonging the lifetime of the catheter, lengthening the interval between required replacements of the lock solution and inhibiting infections in the patient.

In one form, the lock solution of the present invention comprises an amount of a citrate salt to provide an effective catheter lock solution, preferably, but not exclusively, a hypertonic lock solution. The term hypertonic is used herein to refer to a fluid having an osmotic concentration and a density greater than the osmotic concentration and density of the blood of the patient. The lock solution preferably comprises a citrate salt with a concentration range, in weight percent, of from about 1.5% to about 50% with an osmolality of about 300 to about 6400 mOsm. More preferably, the lock solution comprises citrate salt in a concentration range of from about 10% to about 40%, yet more preferably, in a concentration range of from about 20% to about 30%.

In preferred embodiments, the lock solution comprises a citrate salt, and the lock solution is prepared to have sufficient viscosity and density to remain in the lumen for a desired amount of time. It is well known that catheters are manufactured to have a variety of configurations and lumen diameters. For example, catheters can include single or double lumens. The double lumens can be fused adjacent to each other or they can be concentric. The lumens can have varying cross-sectional areas and shapes, ranging from substantially circular to substantially ovoid. A phenomenon common to most lock solutions is that a portion of the solution at the distal end of the lumen diffuses into the patient's blood stream and is replaced in the catheter by blood.

While not intending to be bound by any theory, it is thought that the rate of diffusion of a lock solution from a lumen can be influenced by the cross-sectional shape and area of the particular lumen(s), the density of the lock solution, and the viscosity of the lock solution. Typically, high density lock solutions tend to fall out of the lumen of the catheter, allowing blood to enter into the lumen.

A lock solution of the present invention is preferably prepared to have a viscosity and density such that a substantial portion of the lock solution does not diffuse or flow out of a catheter lumen within about 8 hours. More preferably, the lock solution of the present invention does not diffuse out of a lumen to a substantial extent within about 12 hours, still more preferably within about 24 hours.

In a preferred aspect of the invention, the lock solution of the invention is prepared to have a selected density of from about 1.02 g/ml to about 1.04 g/ml and a viscosity of from about 1.5 centipoise (cP) to about 4.0 cP. More preferably the lock solution has a density of from about 1.02 g/ml to about 1.03 g/ml and a viscosity of from about 1.5 cP to about 2.0 cP. For example in a 10 French TESIO catheter studies with sodium citrate solutions, 46.7% by weight citrate with density of 1.025 and viscosity of 2.0 (by gravity viscometer) where found to remain within the cylindrical catheter for 3 days or more, with the catheter suspended in a solution having viscosity of blood, 13 cP at 37°. In catheters such as the SPLITCATH, with lumens having less hydraulic resistance, this solution will exit the catheter due to gravitational forces. A catheter lock solution

comprising 23% by weight citrate, however, will remain in place for 3 days or more.

The density of the lock solution can be varied by varying the amount of salts included in the solution, with 46.7% being appropriate for 10 French cylindrical catheters, and 23% being appropriate for the double-D shaped lumens of the SPLITCATH.

The viscosity of the lock solution can be varied by adding a viscosifying agent. Viscosifying agents useful with the present invention include those pharmaceutically acceptable agents known or commonly used in treatment of animals including humans. Examples include, but are not limited to, polyethylene glycol, glycerin, polygeline, and non-metabolizable sugars such as sorbitol and mannitol and mixtures of these compounds. An excellent aspect of the invention, therefore is a composition useful as a lock solution that comprises a citrate salt and a viscosifying agent. The viscosifying agent allows a higher concentration of citrate to be used without having egress of the lock solution from the catheter due to high density of the lock solution.

While is understood that optimal viscosity and density are dependent upon the shape and size of a particular lumen, a person of ordinary skill in the art, in view of the description herein, can readily determine a desired density and viscosity for a particular catheter without undue experimentation.

In a preferred embodiment, the lock solution is prepared to have a pH lower than that of the pH of the patient's blood. For example, in humans, the lock solution may advantageously be prepared to have a pH lower than about 6.5, more preferably, the lock solution is prepared to have a pH level of from about 4.5 to about

6.5. Still yet more preferable, the lock solution is prepared to have a pH level of from about 5.0 to about 6.5. The lower the pH, the greater the antibacterial effect of the citrate and the greater the caustic activity in dissolving clots. The pH of the catheter lock solution can be varied by adding either an acid or base according to methods known to those skilled in the art. For example, the pH of the catheter lock solution can be lowered by including a sufficient amount of citric acid to the solution to provide the desired pH level.

An inventive lock solution can be prepared to include a variety of other pharmaceutically acceptable agents. For example, the lock solution can include salts, such as, for example, sodium chloride and sodium heparin. The lock solution can also include a variety of other antibacterial, antimicrobial and anticoagulant agents. Such antibacterial and antimicrobial agents are well known to those skilled in the art and can include, without limitation, gentamicin, vancomycin, and mixtures of these agents. Additional anticoagulant agents include, for example heparin, urokinase, tissue plasminogen activation (tPA)and mixtures of these agents.

By "pharmaceutically acceptable", it is meant that the lock solution and the included salts and other additives which are, within the scope of sound medical judgment, suitable for use in contact with tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with the reasonable benefit/risk ratio. It is also typically necessary that a composition be sterilized to reduce the risk of infection. For example, pharmaceutically acceptable salts are well-known in the

art, for example, as found in S.M. Berge et al. described in detail in *J. Pharmaceutical Science*, 66:1-19, 1977.

In yet another form, the present invention provides a method of inhibiting infections in animals having an indwelling intravascular catheter. A compound having anticoagulant and antibacterial activity is selected, for example, the citrate salt such as trisodium citrate. A lock solution is prepared, including the compound having anticoagulant and antibacterial activity. The resulting lock solution is then infused into the lumen or a catheter.

Thus, the lock solution of the present invention including a citrate salt can be prepared and further include a bactericidal component. In a preferred embodiment, the bactericidal component includes greater than 50% by weight based on the weight of the bactericidal component of the citrate salt. More preferably, the bactericidal component includes greater than about 75%, by weight based on the weight of the component, of the citrate salt. Still more preferably, the bactericidal component includes greater than about 90% of a citrate salt.

Once a lock solution is infused into the lumen of the catheter, it is allowed to remain until that particular catheter or lumen is desired to be accessed again. The lock solution can be flushed directly into the patient without the necessity of removing the fluid before infusing fluids for subsequent treatment. Alternatively, the lock solution can be removed from the catheter prior to infusion or removal of additional fluid for further treatment.

When the lock solution of the present invention is injected into the lumen of the catheter, a sufficient

amount of the lock solution can be injected to substantially fill the lumen of the catheter. Alternatively, a volume less than the amount of fluid needed to fill the catheter can be injected into the lumen. For example, a sufficient amount of lock solution can be injected into the catheter to fill about 80 to about 100% of the internal volume of the catheter. In yet another embodiment, an amount greater than the internal volume of the catheter can be injected. For example, an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the catheter can be injected into the lumen, without adverse effects on the clotting system of the patient.

In yet another embodiment, the lock solution of the present invention can be infused into the lumen or lumens of the indwelling catheter of patients exhibiting a risk of infection. Surgically implanted catheters are used in the treatment of patients exhibiting a variety of health problems. It is well known that certain health problems and/or patients exhibit increased risk of infection based upon historical observation by those skilled in the art. The present invention provides distinct advantages when used on those patients having an increased risk of infection by inhibiting infection in those patients.

In another embodiment, patients are screened for an infection or a substantial risk of infection related to the presence of the catheter. For those patients having such an infection or substantial risk of infection, a catheter lock solution prepared according to the present invention is infused into the lumen of the catheter. The catheter lock includes a citrate salt in a concentration effective to eliminate the

infection and/or reduce the likelihood of subsequent infection.

A lock solution of the present invention has other advantages besides antibacterial properties. If infused into a patient, citrate in the lock solution will be inactivated by calcium in the blood or calcium derived from body stores. When a lock solution having a hypertonic citrate concentration of 47% is used, the total amount of citrate in the lock solution contained in one lumen of a tunneled catheter is approximately 2 ml, containing 3.4 mM of sodium citrate. This amount of citrate is equal to the amount of calcium contained in 1.5 liters of blood. If infused rapidly, this amount of citrate could cause transient hypocalcemic symptoms, but would not anticoagulate the patient. Therefore, if a tunneled catheter is used for fluid infusion for a patient in the emergency room or operating room, the patient will not become anticoagulated just at the time when blood coagulation is important.

In alternative forms the present invention provides a catheter lock infusion device. The infusion device comprises a syringe containing a lock solution prepared according to the present invention. In yet another form the present invention also includes a kit for accessing a patient's intravascular system. The kit includes a catheter having at least one lumen. A container of a catheter lock solution that was prepared according to the present invention is included in the kit. In one embodiment the lock solution includes a viscosifying agent dissolved or dispersed in the lock solution.

For the purpose of promoting further understanding and appreciation of the present invention and its advantages, the following Example is provided. It will be understood, however, that this Example is illustrative and not limiting in any fashion.

Example Illustrating Use of Lock Solutions containing Citrate Salts:

Methods

A study utilizing concentrated citrate in the catheter lock solution was performed on an outpatient dialysis unit (RTC) with 60% of patients having chronic central venous catheters (50 catheters total, the majority ASH SPILTCATH and the remaining TESIO and HICKMAN catheters). At four-month intervals, the citrate concentration in the lock solution was increased from 10% to 20% to 47%. Gentamicin was added at 3 mg/ml to the 10% and the 20% solutions, but not to the 47% citrate solution. The overall incidence of bacteremia in the unit was followed and the amount of urokinase used to open occluded or low-flowing catheters was recorded. The results were compared in incidences of bacteremia and use of urokinase in the unit before the implementation of the lock solution containing citrate salts.

Starting in 1994, all episodes of bacteremia in the outpatient hemodialysis unit were monitored and recorded. Episodes were totaled each month, for all patients, for patients with and without tunneled central venous catheters, and for patients with and without catheter-related explanations for bacteremia. The incidence of bacteremia was calculated as the percent of patients in the unit developing bacteremia

per month ("1%"=1 bacteremic episode per 100 patients in the unit for one month, or 3.3 episodes per 1000 patient-months). The incidence was graphed each month, for the entire period since 1994.

During the period from January 1998 to July 1999, there were 70 patients in this unit, with approximately 60% having tunneled central venous catheters for chronic dialysis (40 catheters total). At the start of the study, the most prevalent catheter in the unit was the Medcomp twin TESIO, though there were a few Bard SOFT CELL catheters. Starting in January 1998, the Medcomp ASH SPLITCATH catheter became the standard tunneled catheter placed in patients beginning dialysis or needing catheter replacement. Almost all of these tunneled catheters were placed using the SITE-RITE ultrasound device for IJ localization. These catheters routinely provided an average blood flow near 300 ml/min.

The average monthly incidence of positive blood cultures in the unit was calculated for the time period from January 1998 through July 1998. During this time period, heparin was used as the standard catheter lock solution, with either 5,000 units or 10,000 units instilled into each lumen at exactly the catheter volume. The incidence of bacteremia during this period was 4.6%, which was higher than the average level since 1994. In August 1998, hemodialysis patients were informed of the plan to change from heparin to sodium citrate/gentamicin as the standard anticoagulant lock for tunneled catheters. From September to December 1998, 10% citrate with 3 mg/ml gentamicin was used as standard catheter lock, injecting slightly more than the catheter volume (2.5 ml total). From January 1999 through April 1999, 20% citrate with 3 mg/ml gentamicin

was the standard catheter lock, injecting slightly more than the catheter volume (2.5 ml total). From May 1999 to July 1999, 47% citrate was the standard catheter lock, injecting exactly the catheter volume. All citrate solutions were made from 47% stock solution, used straight from the 30 ml bottle or in combination with saline and gentamicin. (46.7% trisodium citrate, "triCitrasol", Citra Anticoagulants, Inc., distributed by Ash Medical Systems, West Lafayette, IN). Patients were closely monitored for any evidence of adverse reactions each time the citrate concentration was increased. The monthly incidence of bacteremia was calculated for the 10-month period during which citrate/gentamicin or 47% citrate was used for catheter lock, and compared to the baseline 7-month period by Two-tailed T Test (assuming equal variances).

Also during this time period, the unit use of urokinase (Abbott Laboratories) was monitored. The number of vials of urokinase use by the RTC unit was calculated on a monthly basis. The total number of vials ordered and used by the unit each month in the period from January 1998 through July 1998 was compared to the number of vials used after the conversion to citrate, from September 1998 to July 1999. After May 1999, urokinase became unavailable, but before this time it was available on request. The number of vials used per month in the baseline period was compared to the number of vials after implementation of citrate/gentamicin or 47% citrate catheter lock, by Two-tailed T Test (assuming equal variances).

During the study period, the longevity of tunneled catheters was also investigated, since the prevention of infection of tunneled catheters is less important if

other factors such as clotting or sheath formation limit the life of the catheters. All Ash SPLITCATH catheters placed in end-stage renal disease (ESRD) patients after January 1998 (including patients in two satellite outpatient units) were evaluated and the longevity of the catheters was determined. In all, 57 Splitcath catheters were placed in 57 patients. Failure was defined as any catheter being removed for any complication, whether due to infection or obstruction of flow. Longevity of catheters was determined using lifetable analysis.

Since the outpatient unit has many patients with tunneled catheters, nurses and technicians use utmost care in opening the catheters and connecting to dialysis machines. The caps of the catheter are soaked in betadine for 5 minutes before the caps are removed. Nurses and technicians wear masks and gloves, and the patient wears a mask when the catheter is opened. New protective caps are placed on the catheter following each procedure. Catheters and connectors are inspected for leaks or evidence of damage, each treatment.

Incidence of Bacteremia

The incidence of bacteremia in all 70 patients at the RTC unit was 4.5% of patients per month during the baseline period from January through July of 1998. Following the implementation of hypertonic citrate/gentamicin and then 47% citrate as catheter lock, the incidence of bacteremia decreased significantly to 1.2% (Figure 2, $P<0.001$). There was a downward trend in bacteremia as concentration of citrate was increased from 10 to 20 to 47%. In the

last three months of the study, when 47% citrate was used, the incidence of bacteremia has been zero.

Utilization of Urokinase

The use of urokinase in the dialysis unit during the baseline period was 41 vials per month, or approximately 1 vial per patient with tunneled catheter per month. After implementation of hypertonic citrate/gentamicin then 47% citrate as catheter lock, the use of urokinase decreased to 20 vials per month, about ½ vial per patient with tunneled catheter per month (Figure 3, P=0.02). During the last three months of this study (May, June, July 1999), no urokinase was used for any catheter. In June and July of 1999, urokinase was unavailable at the hospital, and the hospital had not yet substituted syringes of tissue plasminogen activator (tPA) for catheter infusion. However, no catheters were completely occluded or removed for flow problems during these months, so it did not appear that urokinase was required in this month.

Catheter Survival

During the period from January 1998 to July 1999, 57 ASH SPLITCATH catheters were placed in 57 patients in the RTC and satellite units, with an average follow-up of 8 months. One small satellite unit continued using heparin for anticoagulant catheter lock, while the other followed the RTC protocol of increasing citrate catheter lock concentration. During this period, catheters without signs of infection were not removed for bacteremia, but only in patients in whom antibiotic therapy failed to clear signs of infection within 24 hours. Only 3 of the 57 catheters were

removed, 2 for concomitant infection which failed to clear, and one for decreased blood outflow rate. The lifetable analysis of longevity of these catheters indicates a 95% survival at one year (Figure 4). Interventions in these catheters were few, and as discussed above, urokinase use was decreased as hypertonic citrate/gentamicin or 47% citrate were used as catheter lock. Mean catheter flow rate for the Splitcath® catheter remained approximately 300 ml/min during the study, with venous and arterial pressures below 250 mmHg (the pre-defined limit for pressures in these dialysis units).

Conclusions/Discussion

In this study of tunneled catheters in a single dialysis unit, hypertonic citrate (10 or 20%) in combination with gentamicin, or 47% citrate are at least as effective as heparin in preventing clotting of the catheters. The use of urokinase to open these tunneled catheters does not increase, and in fact significantly decreases after implementation of the citrate catheter lock solutions.

Hypertonic citrate as catheter lock appears to decrease the incidence of bacteremia in a dialysis unit with a high percentage of patients with tunneled catheters. When catheters are locked with 10% or 20% citrate containing 3 mg/ml gentamicin, the incidence of bacteremia decreases significantly. An even greater decrease in incidence of bacteremia appears to occur with use of 47% citrate alone (without gentamicin). Through a variety of actions, concentrated citrate is bactericidal and sporicidal when tested in vitro. Therefore, it is expected that it would diminish the

bacterial content of catheters after chance contamination of the catheter hub. On the other hand, a similar antibacterial effect could be obtained through the effect of citrate on biofilm; if the mild corrosive action of citrate helps to eliminate the biofilm, it would also eliminate bacteria trapped within the biofilm. The effect of citrate on bacterial contamination of catheters can decrease risk of bacteremia in patients with catheters without the risk of developing resistant strains of the bacteria (as will occur with antibiotic lock solutions).

Of course, with proper care it is possible to utilize tunneled catheters for dialysis without an antibacterial solution infused. In a satellite outpatient hospital dialysis unit, 20 stable ESRD patients are dialyzed, and the percentage and types of catheters (60% of patients, mostly having mostly SPLITCATH catheters and some TESIO catheters) are similar to those at the RTC unit. The unit uses the same precautions as the RTC unit in handling tunneled catheters. As opposed to the RTC, this unit has traditionally had a very low to zero incidence of bacteremia from any cause. In the period of January 1998 to May 1999, this unit continued to use heparin as catheter lock solution, and had only one patient with bacteremia during this period (representing 5% of all patients, for one month). For all other months the incidence of bacteremia remained zero. Urokinase use also remained low during the entire period.

The problems of infection and occlusion of tunneled catheters for dialysis are paralleled by the smaller catheters used in hospitalized patients with central venous catheters, and in home patients with

long-term TPN, chemotherapeutic and antibiotic administrations. Concentrated citrate may also provide significant advantages in these patients, avoiding catheter clotting, infection and subsequent bacteremia.

The present invention contemplates modification to the infusion device and method of treating patients as would occur to those skilled in the art. It is also contemplated that processes embodied in the present invention can be altered, rearranged, substituted, deleted, duplicated, combined, or added to other processes as would occur to those skilled in the art without departing from the spirit of the present invention. In addition, the various stages, procedures, techniques, phases, and operations within these processes may be altered, rearranged, substituted, deleted, duplicated, or combined as would occur to those skilled in the art. All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference and set forth in its entirety herein.

Further, any theory of operation, proof, or finding stated herein is meant to further enhance understanding of the present invention and is not intended to make the scope of the present invention dependent upon such theory, proof, or finding.

While the invention has been illustrated and described in detail in the drawings and foregoing description, the same is considered to be illustrative and not restrictive in character, it is understood that only the preferred embodiments have been shown and described and that all changes and modifications that come within the spirit of the invention are desired to be protected.

What is claimed is:

1. A method for treating a patient, comprising:

selecting a patient having an indwelling intravascular catheter defining a lumen therethrough and having an infection or a substantial risk of infection related to the presence of the catheter;

infusing a catheter lock solution into the lumen, the solution comprising a citrate salt solution having a concentration effective to eliminate infection and to reduce the likelihood of subsequent infection.

2. The method of claim 1 wherein the lock solution comprises a citrate salt in a concentration range, in weight percent, of between about 1.5% and about 50%.

3. The method of claim 2 wherein the lock solution comprises a citrate salt in a concentration range, in weight percent, of between about 10% and about 40%.

4. The method of claim 3 wherein the lock solution comprises a citrate salt in a concentration range, in weight percent, of between about 20% and about 30%.

5. The method of any of claims 1-4 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

6. The method of any of claims 1-5 wherein the lock solution has a pH level between about 4.5 and about 6.5.

7. The method of any of claims 1-6 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

8. The method of any of claims 1-7 wherein the catheter has an internal volume and said adding includes injecting the catheter with an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

9. A method of inhibiting infections in an animal having an indwelling catheter defining at least one lumen therethrough, said method comprising infusing into the lumen a pharmaceutically acceptable lock solution including a compound having anticoagulant and antibiotic activity, wherein said lock solution has a density and a viscosity sufficient to maintain the lock solution in said lumen for a desired amount of time, wherein the desired amount of time is at least about 8 hours.

10. The method of claim 9 wherein the lock solution includes a citrate salt in a hypertonic concentration range, in weight percent, of between 1.5% and 50%.

11. The method of claim 10 wherein the lock solution includes a citrate salt in a concentration range, in weight percent, of between 10% and 40%.

12. The method of claim 11 wherein the lock solution includes a citrate salt in a concentration range, in weight percent, of between 20% and 30%.

13. The method of any of claims 9-12 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline or mixtures thereof.

14. The method of any of claims 9-13 wherein the lock solution has a density of between about 1.02 g/ml to about 1.04 g/ml and a viscosity of between about 1.5 cP and about 4.0 cP.

15. The method of any of claims 9-14 wherein the lock solution has a density of between about 1.02 g/ml and about 1.03 g/ml a viscosity of between about 1.5 cP and about 2.0 cP.

16. The method of any of claims 9-15 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

17. The method of any of claims 9-16 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of

the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

18. The method of any of claims 9-17 wherein the lock solution has a pH level between about 4.5 and about 6.5.

19. A method of treating animals having a surgically implanted catheter, said method comprising infusing into said catheter a pharmaceutically acceptable lock solution comprising a bactericidal component, said bactericidal component including greater than about 50%, by weight based on the weight of the bactericidal component, of a citrate salt.

20. The method of claim 19 wherein the bactericidal component includes greater than about 75%, by weight based on the weight of the bactericidal component, of a citrate salt.

21. The method of claim 19 or 20 wherein the bactericidal component includes greater than about 90%, by weight based on the weight of the bactericidal component, of a citrate salt.

22. The method of any of claims 19-21 wherein the lock solution includes a viscosifying agent.

23. The method of any of claims 19-22 wherein the pharmaceutically acceptable lock solution has a pH between about 4.5 and about 6.5.

24. The method of any of claims 19-23 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

25. The method of any of claims 19-24 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

26. An infusion device for infusing a lock solution into a lumen of a catheter, said device comprising:

a syringe;

a pharmaceutically acceptable lock solution contained within the syringe, said lock solution comprising a citrate salt;

wherein said syringe containing the lock solution is sterilized.

27. The device of claim 26 wherein said lock solution comprising a citrate salt.

28. The device of claim 26 or 27 wherein the lock solution comprises a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

29. The device of any of claims 26-28 wherein the lock solution has a density of between about 1.0 and about 1.5 and a viscosity of between about 1.5 cP and 4.0 cP.

30. A device comprising:

an intravascular catheter having at least one lumen; and

a pharmaceutically acceptable lock solution positioned within the lumen, said lock solution comprising a citrate salt, wherein said lock solution has a pH level below about 6.5.

31. The device of claim 30 wherein said citrate salt comprises a sodium citrate salt.

32. The device of claim 30 or 31 wherein the lock solution has a pH level between about 4.5 and about 6.5.

33. The device of any of claims 30-32 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

34. The device of any of claims 30-33 wherein the lock solution has a density between about 1.0 and about 1.5 and a viscosity between about 1.5 cP and about 4.0 cP.

35. A kit for accessing a patient's intravascular system, comprising:

a catheter defining therethrough at least one lumen;

a container; and

a catheter lock solution contained within the container, the solution comprising a citrate salt solution and a viscosifying agent dissolved or dispersed in the solution.

36. The kit according to claim 35 wherein said container is a syringe.

37. A catheter lock fluid comprising an aqueous solution of a citrate salt and a viscosifying agent dissolved or dispersed in the solution.

38. The fluid according to claim 37 wherein the viscosifying agent is selected from the group consisting of polyethylene glycol, glycerin, polygeline and mixtures thereof.

39. A composition comprising an aqueous lock solution including, in weight percent, about 1.5% to about 50% of a citrate salt, and an amount of a viscosifying agent sufficient provide the lock solution with a viscosity of from about 1.0 cP to about 4.0cP.

40. The composition of claim 39 wherein the lock solution has a pH level between about 4.5 and about 6.5.

41. The composition of claim 39 or 40 wherein the lock solution includes, in weigh percent, about 10% to about 40% of the citrate salt.

42. The composition of any of claims 39-41 wherein the citrate salt is trisodium citrate.

43. The composition of any of claims 39-42 comprising heparin.

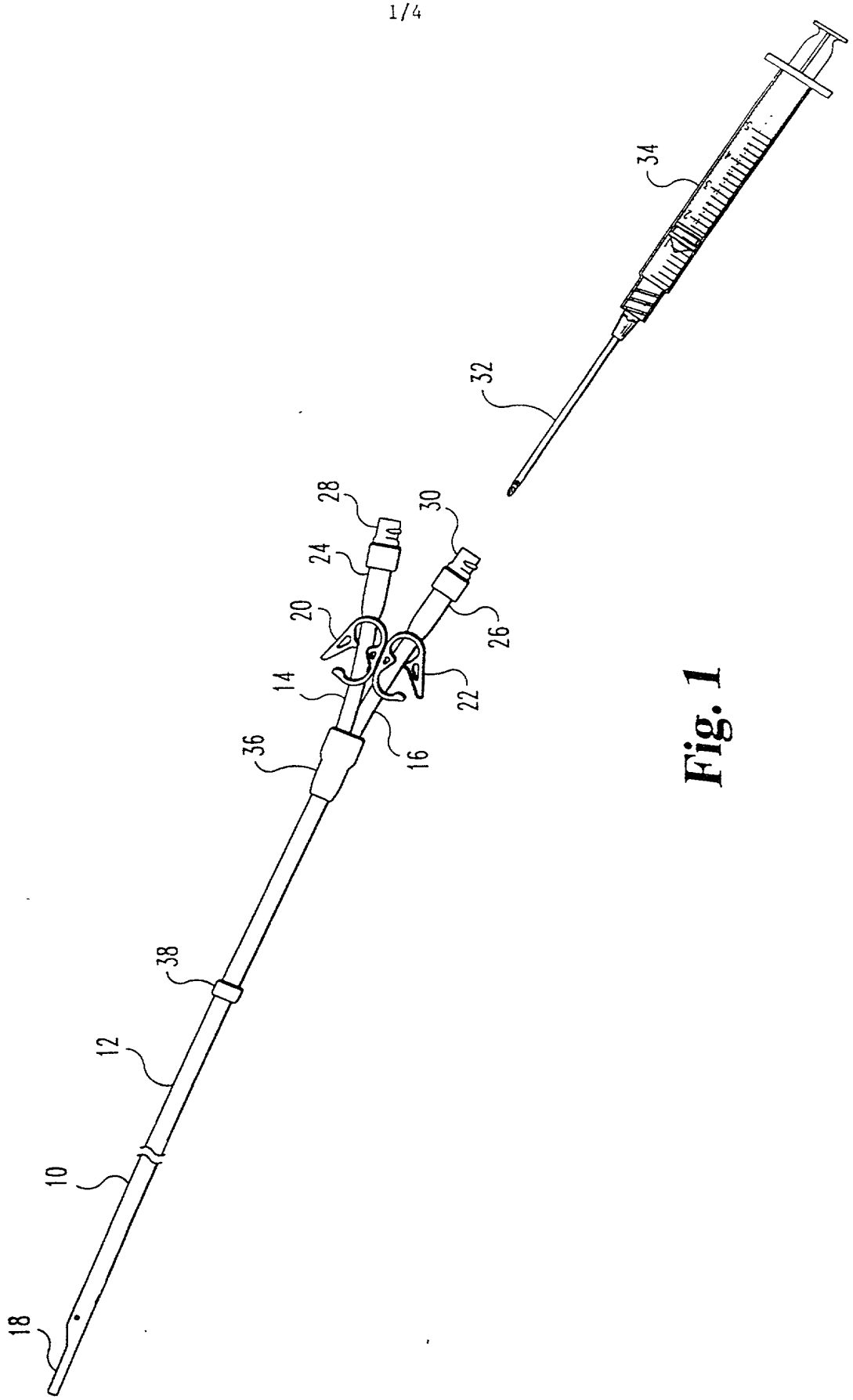


Fig. 1

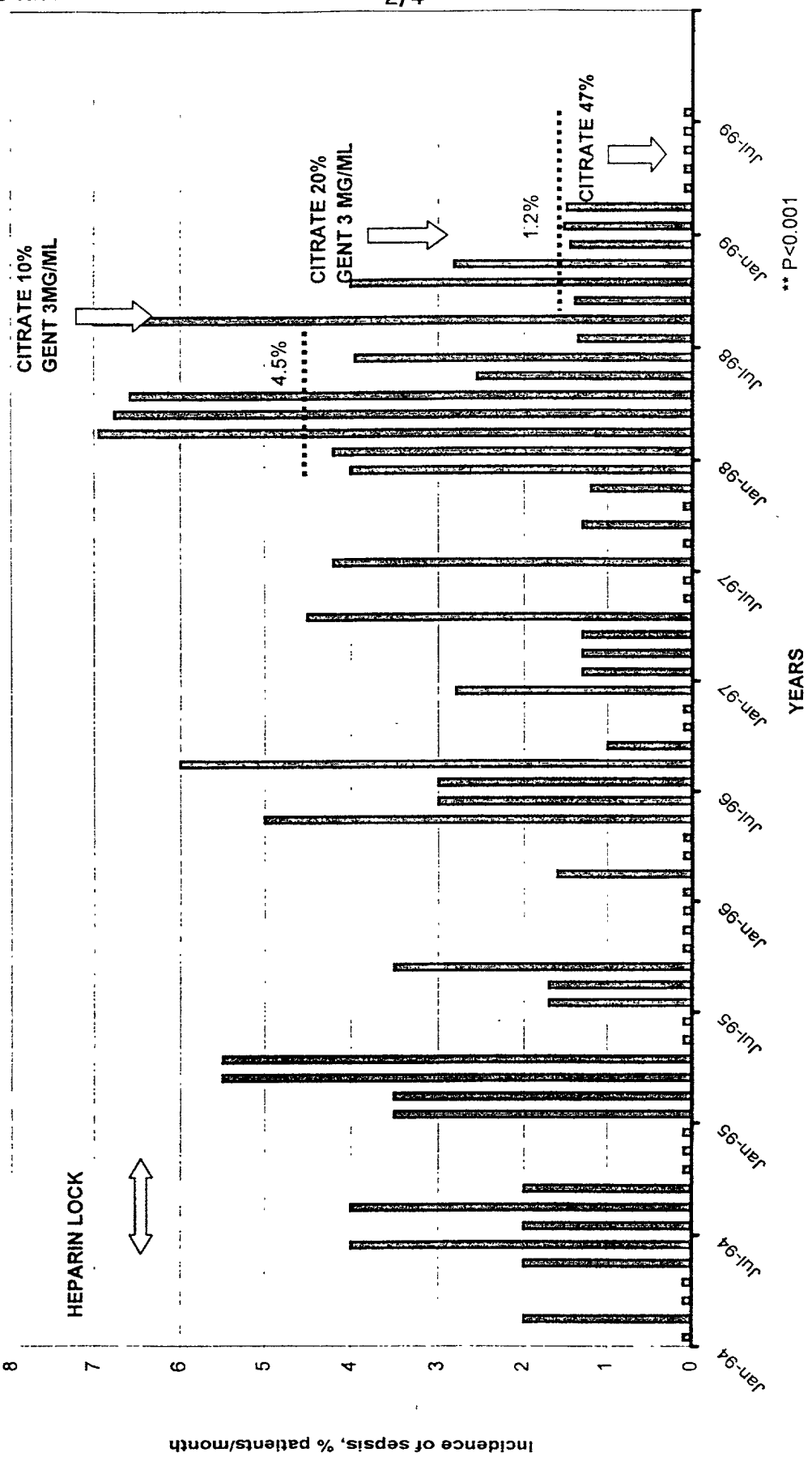


FIGURE 2
MONTHLY INCIDENCE OF SEPSIS IN ALL PATIENTS, RTC UNIT

Figure 3

Vials of Urokinase Used For Catheter Occlusion

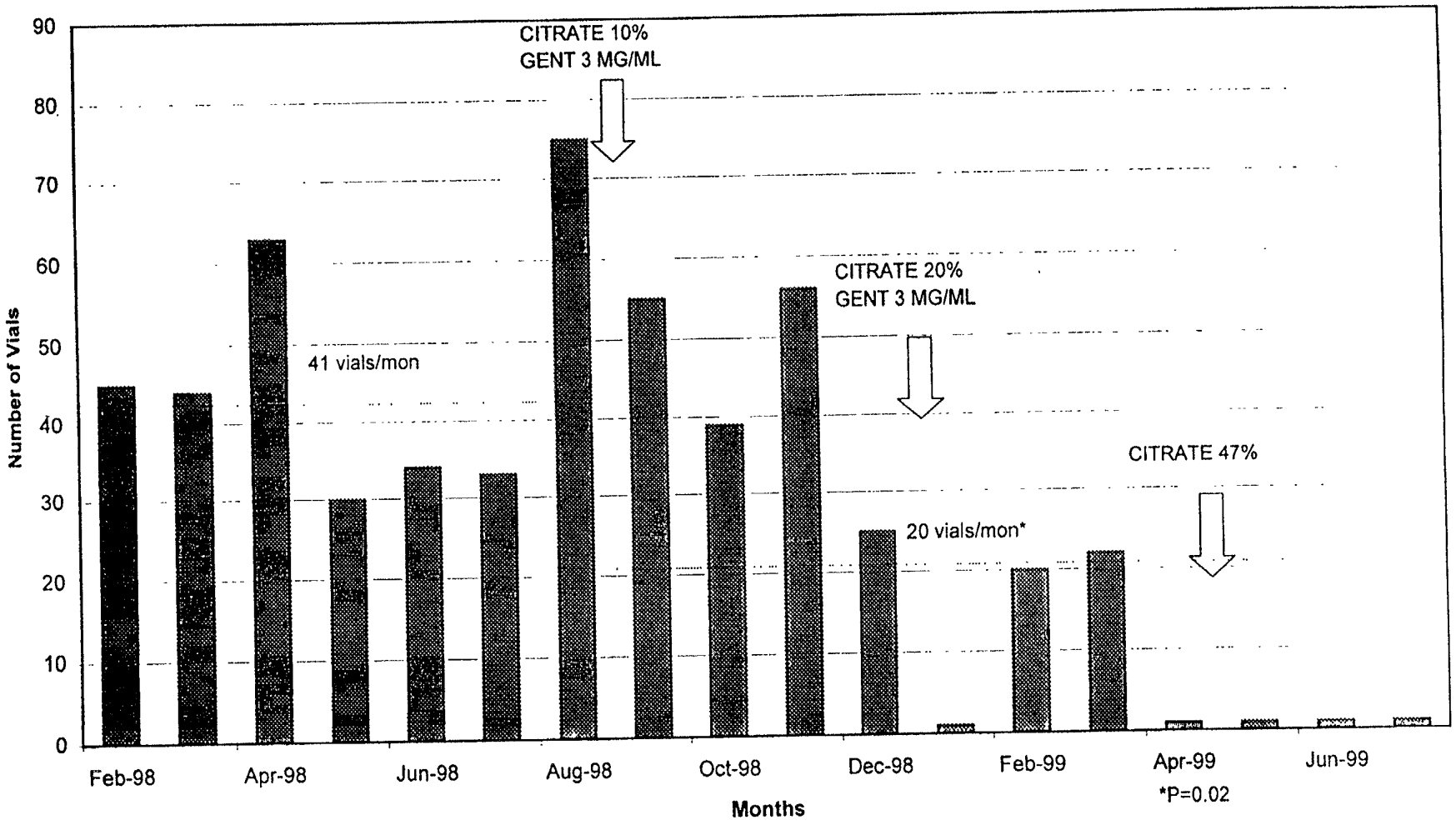
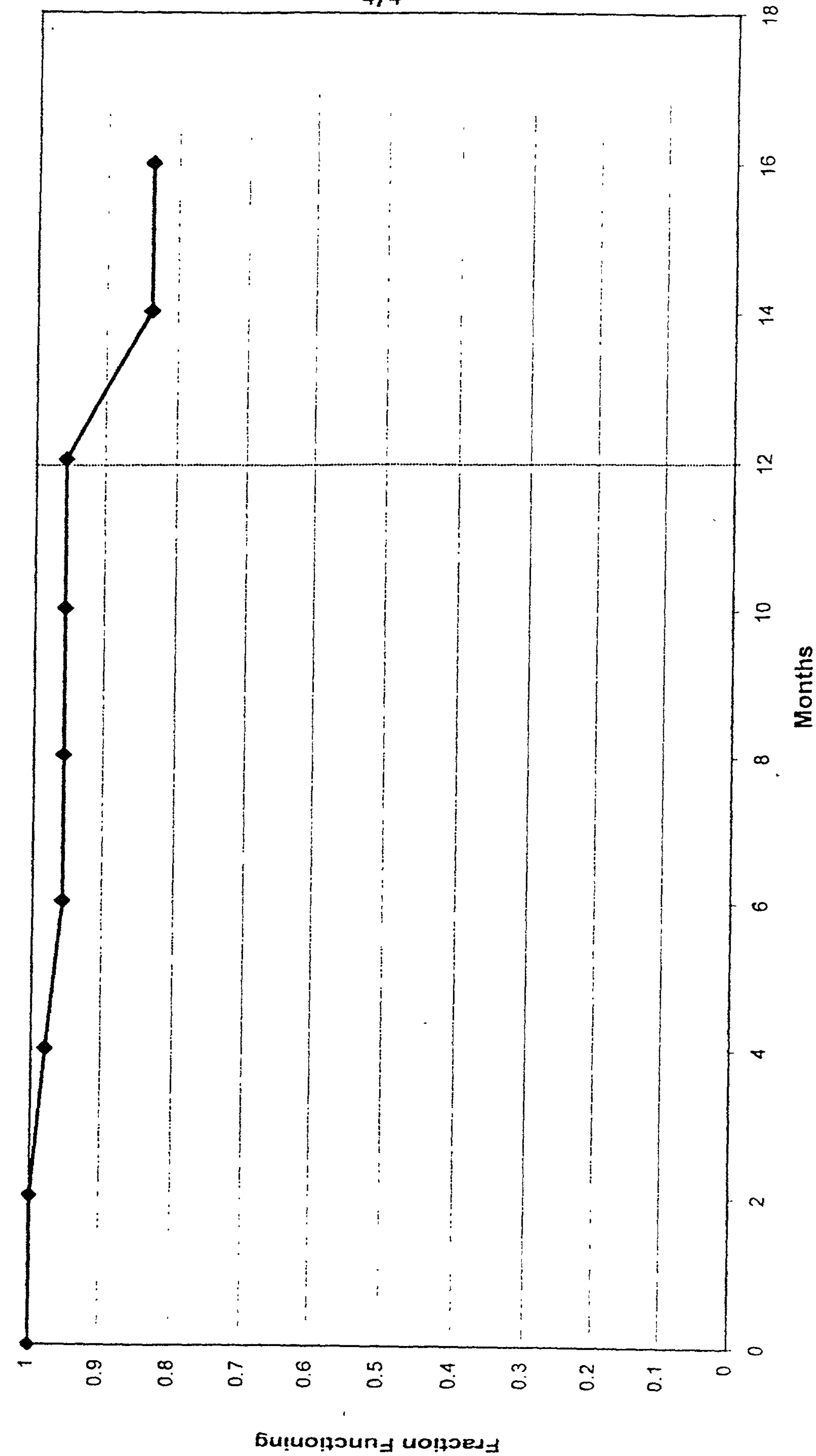


FIGURE 4
Longevity of Splitcath Catheters



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WENMM SB/01 (4-99)/ #124331

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing **OR** ☒ Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e) required)

Attorney Docket Number	**11020-55**
First Named Inventor	**Stephen R. Ash**
COMPLETE IF KNOWN	
Application Number	**09/763,666**
Filing Date	**February 23, 2001**
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD OF ENHANCING CATHETER PATENCY USING A CITRATE SALT CATHETER LOCK SOLUTION

(Title of the Invention)

the specification of which

☐ is attached hereto **OR** [X] was filed on (MM/DD/YYYY) 02/23/2001 as United States Application Number 09/763,666 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim, as amended by any amendment specifically referred to above.

I acknowledge and hereby disclose information which is material to patentability as defined in 37 CFR 1 56.

I hereby claim foreign priority benefits under 35 U.S.C. 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Check Only If Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

I hereby claim the benefit under 35 U S.C. 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/097,777	08/25/1998	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

DECLARATION – Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the Untied States of America, listed below, and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S C 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (*if applicable*)
PCT/US99/19307	08/25/1999	

[ ] Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

As a named inventor, I hereby appoint the following registered practioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

[ ] Customer Number [ ] → *Place Customer Number Bar Code Label Here*

OR

[X] Registered practioner(s) name/registration number listed below.

Name	Registration Number	Name	Registration Number
GREGORY B. COY	40,967		

[X] Additional registered practioner(s) named on supplemental Registered Practioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to : [ ] Customer Number Bar Code Label [ ] *OR* [X] Correspondence address below

Name	GREGORY B. COY				
Address	WOODARD EMHARDT NAUGHTON MORIARTY & McNETT				
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City	Indianapolis	**State**	IN	**ZIP**	46204
Country	US	**Telephone**	317/ 634-3456	**Fax**	317/637-7525

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: [ ] A petition has been filed for this unsigned inventor.

Given Name (first and middle [if any])	Family Name or Surname
Stephen R.	Ash

Inventor's Signature	Stephen R Ash						Date	May 15, 2001	
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Post Office Address									
City	Lafayette	State	Indiana	ZIP	47905	Country	US		

[ ] **Additional inventors are being name on the _____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.**

Type a Plus sign (+) inside this box → [+]

WENMM SB/02C (4/01)

DECLARATION

Registered Practitioner Information (Supplemental Sheet)

Name	Registration Number	Name	Registration Number
Harold R. Woodard	16,214		
C. David Emhardt	18,483		
Joseph A. Naughton, Jr.	19,814		
John V. Moriarty	26,207		
John C. McNett	25,533		
Thomas Q. Henry	28,309		
James M. Durlacher	28,840		
Charles R. Reeves	28,750		
Vincent O. Wagner	29,596		
Steve Zlatos	30,123		
Spiro Bereveskos	30,821		
William F. Bahret	31,087		
Clifford W. Browning	32,201		
R. Randall Frisk	32,221		
Daniel J. Lueders	32,581		
Kenneth A. Gandy	33,386		
Timothy N. Thomas	35,714		
Kerry P. Sisselman	37,237		
Kurt N. Jones	37,996		
John H. Allie	39,088		
Holiday W. Banta	40,311		
Troy J. Cole	35,102		
L. Scott Paynter	39,797		
J. Andrew Lowes	40,706		
Charles J. Meyer	41,996		
Matthew R. Schantz	40,800		
Gregory B. Coy	40,967		
Lisa A. Hiday	40,036		
John V. Daniluck	40,581		
Christopher A. Brown	41,642		
C. John Brannon	44,557		
Jason J. Schwartz	43,910		
Arthur J. Usher IV	41,359		
Douglas A. Collier	43,556		
Brad A. Schepers	45,431		
Scott J. Stevens	29,446		
James B. Myers	42,021		
John M. Bradshaw	46,573		
C. Amy Ng Smith	42,931		
Charles P. Schmal	45,082		
Edward E. Sowers	36,015		